

DIALOG

15/3,AB/1 (Item 1 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)  
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09612997 98054343 PMID: 9391135

Respiratory syncytial virus ( RSV) SH and G proteins are not essential for viral replication in vitro: clinical evaluation and molecular characterization of a cold-passaged, attenuated RSV subgroup B mutant.

Karron RA; Buonagurio DA; Georgiu AF; Whitehead SS; Adamus JE; Clements-Mann ML; Harris DO; Randolph VB; Udem SA; Murphy BR; Sidhu MS  
Center for Immunization Research, Department of International Health, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD 21205, USA. rkarron@jhsp.h.edu

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 9 1997, 94 (25) p13961-6, ISSN 0027-8424  
Journal Code: PV3

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Languages: ENGLISH

Document type: Journal Article

Record type: Completed

A live, cold-passaged (cp) candidate vaccine virus, designated **respiratory syncytial virus (RSV)** B1 cp-52/2B5 (cp-52), replicated efficiently in Vero cells, but was found to be overattenuated for RSV-seronegative infants and children. Sequence analysis of reverse-transcription-PCR-amplified fragments of this mutant revealed a large **deletion** spanning most of the coding sequences for the small hydrophobic ( SH ) and attachment (G) proteins. Northern blot analysis of cp-52 detected multiple unique read-through mRNAs containing SH and G sequences, consistent with a **deletion mutation** spanning the SH :G gene junction. Immunological studies confirmed that an intact G glycoprotein was not produced by the cp-52 virus. Nonetheless, cp-52 was infectious and replicated to high titer in tissue culture despite the absence of the viral surface SH and G glycoproteins. Thus, our characterization of this negative-strand RNA virus identified a novel replication-competent **deletion** mutant lacking two of its three surface glycoproteins. The requirement of SH and G for efficient replication in vivo suggests that selective **deletion** of one or both of these RSV genes may provide an alternative or additive strategy for developing an optimally attenuated vaccine candidate.

15/3,AB/8 (Item 2 from file: 349)  
DIALOG(R) File 349:PCT Fulltext  
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00511883

PRODUCTION OF INFECTIOUS RESPIRATORY SYNCYTIAL VIRUS FROM CLONED NUCLEOTIDE SEQUENCES  
PRODUCTION DE VIRUS SYNCYTIAL RESPIRATOIRE INFECTIEUX A PARTIR DE SEQUENCES DE NUCLEOTIDES CLONES

Patent Applicant/Assignee:

THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE COLLINS Peter L

Inventor(s):

COLLINS Peter L

Patent and Priority Information (Country, Number, Date):

Patent: WO 9712032 A1 19970403

Application: WO 96US15524 19960927 (PCT/WO US9615524)

Priority Application: US 957083 19950927

Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO

# DIALOG

NZ PL PT RO RU SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM  
AZ BY KG KZ MD TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF  
BJ CF CG CI CM ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 16569

## English Abstract

Isolated polynucleotide molecules provide **RSV** genome and antigenomes, including that of human, bovine or murine **RSV** or **RSV** -like viruses, and chimera thereof. The recombinant genome or antigenome can be expressed with a nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large (L) polymerase protein, and an RNA polymerase elongation factor to produce isolated infections **RSV** particles. The recombinant **RSV** genome and antigenome can be modified to produce desired phenotypic changes, such as attenuated viruses for vaccine use.

## Japanese Abstract

Cette invention concerne des molecules de polynucleotides isolees permettant d'obtenir des genomes et antigenomes de VSR, y compris ceux de VSR humains, bovins et murins ou de virus de type VSR, ainsi que leurs chimeres. Le genome ou antigenome recombine peut etre exprime a l'aide d'une proteine a nucleocapside (N), d'une phosphoproteine a nucleocapside (P), d'une proteine de polymerase de grande taille (L) et d'un facteur d'allongement d'ARN polymerase afin de produire des particules de VSR infectieuses isolees. Les genome et antigenome de VSR recombines peuvent etre modifies afin de produire les changements phenotypiques voulus, tel que des virus affaiblis pouvant etre utilises dans des vaccins.

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18/3,AB/1 (Item 1 from file: 155)  
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09646998 98105793 PMID: 9445048

**The NS1 protein of human respiratory syncytial virus is a potent inhibitor of minigenome transcription and RNA replication.**

Atreya PL; Peeples ME; Collins PL

Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-0720, USA.

Journal of virology (UNITED STATES) Feb 1998, 72 (2) p1452-61,  
 ISSN 0022-538X Journal Code: KCV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The **NS1** protein (139 amino acids) is one of the two nonstructural proteins of human respiratory syncytial virus (RSV) and is encoded by a very abundant mRNA transcribed from the promoter-proximal RSV gene. The function of **NS1** was unknown and was investigated here by using a reconstituted transcription and RNA replication system that involves a minireplicon and viral proteins (N, P, L and M2-1) expressed from separate cotransfected plasmids. Coexpression of the **NS1** cDNA strongly inhibited transcription and RNA replication mediated by the RSV polymerase, even when the level of expressed **NS1** protein was substantially below that observed in RSV-infected cells. The effect depended on synthesis of **NS1** protein rather than **NS1** RNA alone. Transcription and both steps of RNA replication, namely, synthesis of the antigenome and the genome, appeared to be equally sensitive to inhibition. The efficiency of encapsidation of the plasmid-derived minigenome was not altered by coexpression of **NS1**, indicating that the inhibition occurs at a later step. In two different dicistronic minigenomes, transcription of each gene was equally sensitive to inhibition by **NS1**. This suggested that the gradient of transcriptional polarity was unaffected and that the effect of **NS1** instead probably involves an early event such as polymerase entry on the genome. **NS1**-mediated inhibition of transcription and RNA replication was not affected by coexpression of the M2 mRNA, which has two open reading frames encoding the transcriptional elongation factor M2-1 and the putative negative regulatory factor M2-2. The potent nature of the **NS1**-mediated inhibition suggests that negative regulation is an authentic function of the **NS1** protein, albeit not necessarily the only one.

18/3,AB/3 (Item 1 from file: 399)  
 DIALOG(R) File 399:CA SEARCH(R)  
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128151668 CA: 128(13)151668m PATENT

**Attenuated respiratory syncytial virus with a temperature-sensitive mutation in the polymerase and their use in vaccines**

INVENTOR(AUTHOR): Murphy, Brian R.; Collins, Peter L.; Whitehead, Stephen S.; Bukreyev, Alexander A.; Juhasz, Katalin; Teng, Michael N.

LOCATION: USA

ASSIGNEE: United States Dept. of Health and Human Services; Murphy, Brian R.; Collins, Peter L.; Whitehead, Stephen S.; Bukreyev, Alexander A.; Juhasz, Katalin; Teng, Michael N.

PATENT: PCT International ; WO 9802530 A1 DATE: 19980122

APPLICATION: WO 97US12269 (19970715) \*US 21773 (19960715) \*US 46141 (19970509) \*US 47634 (19970523)

PAGES: 242 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-007/04A;

DIALOG

C12N-007/01B; A61K-039/155B; C12N-015/45B; C12N-007/00B

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG

18/3,AB/5 (Item 2 from file: 349)

DIALOG(R) File 349:PCT Fulltext

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00511883

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**PRODUCTION DE VIRUS SYNCYTIAL RESPIRATOIRE INFECTIEUX A PARTIR DE SEQUENCES DE NUCLEOTIDES CLONES**

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English Abstract

Isolated polynucleotide molecules provide RSV genome and antigenomes, including that of human, bovine or murine RSV or RSV-like viruses, and chimera thereof. The recombinant genome or antigenome can be expressed with a nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large (L) polymerase protein, and an RNA polymerase elongation factor to produce isolated infectious RSV particles. The recombinant RSV genome and antigenome can be modified to produce desired phenotypic changes, such as attenuated viruses for vaccine use.

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DIALOG

21/3,AB/1 (Item 1 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)  
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09345701 97332323 PMID: 9188557

**Analysis of the gene start and gene end signals of human respiratory syncytial virus : quasi-templated initiation at position 1 of the encoded mRNA.**

Kuo L; Fearn R; Collins PL  
Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892-0720, USA.  
Journal of virology (UNITED STATES) Jul 1997, 71 (7) p4944-53,  
ISSN 0022-538X Journal Code: KCV  
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Document type: Journal Article  
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The gene start (GS) and gene end (GE) transcription signals of human respiratory syncytial virus (RSV) strain A2 were analyzed in helper-dependent monocistronic and dicistronic minireplicons which were complemented by a standard RSV strain. The GS signal, which is the start site for mRNA synthesis, is highly conserved for the first nine genes: 3'-CCCCGUUUA(U/C) (negative sense). This conserved version of the signal was analyzed by "saturation" mutagenesis, in which all 10 positions, as well as one downstream and one upstream position, were changed one at a time into each of the other three nucleotides. Most of the positions appear to contribute to the signal: positions 1, 3, 6, 7, and, in particular, 9 were the most sensitive, whereas position 5 was relatively insensitive. The effect of nucleotide substitution in the first position of the signal was examined further by cDNA cloning and sequence analysis of the residual mRNA which was produced. For the two mutants examined (1C to U, and 1C to A), the site of initiation was unchanged. However, the mRNAs were dimorphic with regard to the assignment of the 5'-terminal nucleotide: two-thirds contained the predicted mutant substitution, and one-third contained the parental assignment. Intracellular minigenome contained only the mutant assignment, indicating that the heterogeneity was at the level of transcription by the RSV polymerase. This suggests that the templated mutant assignment at position 1 can sometimes be overridden by an innate preference for the parental assignment, a phenomenon which we dubbed quasi-templated initiation. The GS signal of the L gene, encoding the 10th RSV mRNA, contains three differences (3'-CCCUGUUUUA) compared to the conserved version. It was shown to be equal in efficiency to the conserved version. This was unexpected, since the saturation mutagenesis described above indicated that U in place of A at position 9 should be highly inhibitory. Instead, the A at position 10 of the L GS signal was found to be critical for activity, indicating that an essential A residue indeed was present in both versions of the GS signal but that its spacing differed. The GE signal, which directs termination and polyadenylation, has more sequence diversity in nature than does the GS signal. The naturally occurring GE signals of strain A2 were compared by their individual incorporation into a dicistronic minigenome. They were similar in the ability to produce translatable mRNA except in the cases of NS1 and NS2, which were approximately 60% as efficient.

21/3,AB/2 (Item 1 from file: 399)  
DIALOG(R) File 399:CA SEARCH(R)  
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128151668 CA: 128(13)151668m PATENT  
**Attenuated respiratory syncytial virus with a temperature-sensitive mutation in the polymerase and their use in vaccines**

DIALOG

INVENTOR(AUTHOR): Murphy, Brian R.; Collins, Peter L.; Whitehead, Stephen S.; Bukreyev, Alexander A.; Juhasz, Katalin; Teng, Michael N.

LOCATION: USA

ASSIGNEE: United States Dept. of Health and Human Services; Murphy, Brian R.; Collins, Peter L.; Whitehead, Stephen S.; Bukreyev, Alexander A.; Juhasz, Katalin; Teng, Michael N.

PATENT: PCT International ; WO 9802530 A1 DATE: 19980122

APPLICATION: WO 97US12269 (19970715) \*US 21773 (19960715) \*US 46141 (19970509) \*US 47634 (19970523)

PAGES: 242 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-007/04A; C12N-007/01B; A61K-039/155B; C12N-015/45B; C12N-007/00B

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG

21/3,AB/5 (Item 1 from file: 654)

DIALOG(R)File 654:US PAT.FULL.

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02719054

Utility

**RESPIRATORY SYNCYTIAL VIRUS RIBOZYMES**

[ Enzymatic RNA molecule which specifically cleaves genomoc RNA of respiratory syncytial virus or messenger RNA encoded by said virus in specified region]

PATENT NO.: 5,693,532

ISSUED: December 02, 1997 (19971202)

INVENTOR(s): McSwiggen, James, Boulder, CO (Colorado), US (United States of America)

Draper, Kenneth, Boulder, CO (Colorado), US (United States of America)

Pavco, Pam, Layfayette, CO (Colorado), US (United States of America)

Woolf, Tod, Watertown, MA (Massachusettes), US (United States of America)

ASSIGNEE(s): Ribozyme Pharmaceuticals, Inc , (A U.S. Company or Corporation), Boulder, CO (Colorado), US (United States of America)

[Assignee Code(s): 38218]

EXTRA INFO: Assignment transaction [Reassigned], recorded July 16, 1999 (19990716)

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FILED: November 04, 1994 (19941104)

FULL TEXT: 9842 lines

ABSTRACT

An enzymatic RNA molecule which cleaves respiratory syncytial virus (RSV) genomic and RSV encoded RNA.

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